



# JRC TECHNICAL REPORT

## Smoking and COVID-19

A review of studies  
suggesting a protective effect  
of smoking against COVID-19

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## Summary

The risk factors for contracting symptomatic COVID-19 are not yet fully understood, age and certain underlying health conditions are considered to be detrimental in this respect. Case studies revealed an astonishingly low number of current smokers among patients suffering from symptomatic COVID-19 compared to the general population, leading to the conclusion that smoking/nicotine uptake might have a preventive effect. This is difficult to understand seeing that studies found an increased expression of the angiotensin-converting enzyme (ACE-2) in smokers, the entrance gate of the coronavirus into human cells. Consequently, the use of the proportion of smokers in the general population as a reference for deriving prevalence ratios to study the association of smoking with COVID-19 disease outcomes may be inappropriate. Prevalence data for smoking and comorbidities (hypertension, diabetes mellitus, and chronic obstructive pulmonary disease) reported in 25 studies, which partially identified a potentially beneficial effect of smoking/nicotine intake, were re-analysed to investigate the relationship between COVID-19 mortality and national smoking prevalence taking account of known risk factors associated with mortality. The limited agreement of the prevalence of those risk factors in the general population with the cohort data demonstrates indirectly that these patients most likely do not reflect the health status of the general population. In the absence of specifically designed studies, any hypothesis on the effect of nicotine on symptomatic COVID-19 remains speculative. The number of potentially confounding variables would require a multivariate statistical approach and large cohort sizes for providing clarity on the significance of potential effects. However, the structure of the published aggregated data permits only univariate approaches. As such, the hypothesis of a potentially protective effect of nicotine on symptomatic COVID-19 cannot be verified.

## **Introduction**

The conclusions from a cross sectional study conducted by French scientist that smoking might protect against symptomatic infections with the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused both a lot of attention in public media and shockwaves among tobacco control organisations (1). The response of the public, exposed to uncertainty and fear about SARS-CoV-2 infections, was so massive, that the French Ministry of Health imposed on 23 April 2020 temporary restrictions on the sale of nicotine supplying therapeutics, which are usually used in smoking cessation therapy (2, 3). The respective ministerial decree reasoned the measure with prevention of self-medication and overdosing of nicotine, and ascertaining an uninterrupted supply of the products for therapeutic purposes. There is also anecdotal information about an increase in cigarette prices in Iran, due to an increased demand of tobacco products after the publication of the French study. France, however, declared at the virtual meeting of the G7 health ministers to further study the potentially positive effect of nicotine in fighting the coronavirus disease 2019 (COVID-19).

It is without surprise that the tobacco control community issued warnings and advised strongly against (commencing) smoking for preventing COVID-19.

Questions, which have to be addressed in this context, are whether smoking, respectively nicotine uptake, have any effect on COVID-19, and if so, what is the magnitude of the effect. Press reports relating the low number of smokers with symptomatic COVID-19 to beneficial effects of smoking do not properly reflect the current scientific debate, which centres on physiological effects of nicotine uptake and not on smoking.

It has to be noted that most publications on the possible link between smoking (nicotine consumption) and COVID-19 outcomes provide plausible hypotheses, but lack experimental evidence. Much of the relevant information is still under peer review and published on pre-print portals only.

## **Nicotine, the Renin-Angiotensin System and COVID-19**

There is large agreement in the scientific community that SARS-CoV-2 enters host cells via the angiotensin-converting enzyme 2 (ACE2), a transmembrane protein with both extracellular and intracellular components (4-7). ACE2 is part of the renin-angiotensin system (RAS), which exerts different functions in the human body, among them it is involved in the regulation of blood pressure (8). Downregulation of ACE2 in virus-infected cells triggers a response of the immune system, including the production of pro-inflammatory cytokines, which can lead to a so-called 'cytokine storm' resulting in multi-organ failure and, ultimately, leading to death (6).

Any intervention in the homeostasis of the RAS system may have consequences regarding the susceptibility to SARS-CoV-2 infections and outcomes of COVID-19. Pharmaceutical interventions and environmental as well as individual behavioural factors, such as nicotine consumption via smoking, could intervene in RAS homeostasis (9, 10).

Nicotine binds in the human body to the nicotinic acetylcholine receptor, which is expressed in many body tissues. Several biochemical mechanisms are used to explain a hypothetical effect of nicotine on COVID-19 outcomes and the low prevalence of smokers among hospitalised COVID-19 patients:

- A nicotine dependent downregulation of the expression of the ACE2 receptor in several body tissues could limit the number of entry gates for SARS-CoV-2.
- The inhibitory effect of nicotine on the production of pro-inflammatory cytokines, which led to adverse outcomes in COVID-19 patients if released in overwhelming amounts ("cytokine storm").
- The immune system of current smokers might be more tolerant and less prone to the over-production of immune cells and cytokines compared to immunocompetent non-smokers, reducing thereby the likelihood of the development of acute respiratory distress syndrome (ARDS).

Contrary to the described effects, several authors found higher ACE2 gene expression levels in small airway epithelial cells of smokers and COPD patients compared to former smokers and never smokers (11, 12).

## Smoking and COVID-19

The basis for triggering a debate regarding a possible beneficial effect of smoking is formed by several retrospective studies on clinical characteristics and comorbidities of hospitalized COVID-19 patients (1, 13-37).

Earlier meta-analyses aimed to elucidate the effect of smoking on the prevalence and severity of COVID-19 (35, 38-43). They analysed studies with large differences in cohort sizes and inconsistent endpoints (Table 1). Only Vardavas and Nikitara (Relative Risk<sup>1</sup> (RR)=2.4; 95% CI 1.43-4.04) and Farsalinos et al. (Odds Ratio<sup>2</sup>=1.53; 95% CI 1.06-2.20) demonstrated that the severity of the illness and the fatality rate of active smoker hospitalised for COVID-19 is worse compared to non-smokers (38, 43). The majority of meta-analyses did not identify statistically significant effects, or only a questionable effect of smoking on the severity of COVID-19 (39-41). The latter was observed in a meta-analysis of case studies by Zhao et al., who reported for active smokers a doubling of the risk to develop severe COVID-19 compared to non-smokers (weighted odd ratio of about two), which vanished after breaking down and compiling studies according to differences in endpoints (40).

Contrary to meta-analyses that resulted in either no observable effects of smoking or a negative influence on the progression of COVID-19, several meta-analyses pointed out that the number of smokers among hospitalised COVID-19 patients was low in comparison to the smoking habits of the underlying general population. The very same was reported by Simons et al. (44) in their most recent version of the living rapid evidence review on the association of smoking status with SARS-CoV-2 infection, hospitalisation and mortality from COVID-19. The sixth version of this living rapid evidence review compiles information from 174 observational studies stratified by smoking status.

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<sup>1</sup> RR compares the risk of a health event (disease or death) among one group with the risk among another group. A risk ratio of 1.0 indicates identical risk among the two groups.

<sup>2</sup> OR represents the odds that an outcome will occur given a particular exposure, compared to the odds of the outcome occurring in the absence of that exposure.

Table 1: Overview on meta-analyses

	<b>Studies</b>	<b>Subjects</b>	<b>Former Smoker</b>	<b>Endpoint</b>	<b>Indicator</b>	<b>Pooled Effect*</b>
<b>Lippi et al. (39)</b>	5	1399	No information	Severe/non-severe COVID-19	OR	OR=1.69 (0.41-6.92)
<b>Vardavas &amp; Nikitara (38)</b>	5	1549		1) Severe/non-severe COVID-19,	1) RR	1) RR=1.4 (0.98-2.00)
				2) ICU admission, mechanical ventilation, death	2) RR	2) RR=2.4 (1.43-4.04)
<b>Farsalinos Barbouni Niaura (42)</b>	13	5960	1) Left out	Smoking prevalence	P	1) P=6.5% (4.9%-8.2%)
			2) Pooled with smoker			2) P=7.3% (5.7%-8.9%)
<b>Farsalinos et al. (43)</b>	18	6515	Included in non-current smoking	1) Current smoking	1) POR	1) POR=0.20 (0.16-0.25)
				2) Adverse outcome	2) OR	2) OR=1.53 (1.06-2.20)
<b>Zhao et al. (40)</b>	7	1726	Included in non-smoker	Severity of COVID-19	OR	OR=1.97 (0.95-0.27)
	1) 4	1) 1216		1) Subgroup ISU, Ventilation or death	1) OR	1) OR=1.43 (0.49-4.22)
	2) 3	2) 329		2) Severe COVID-19 or disease progression	2) OR	2) OR=2.86 (0.73-11.24)
<b>Gonzales Rubio et al. (41)</b>	18	7671	Included in non-smoker	Smoking prevalence	OR	OR=0.18 (0.14-0.22)

OR: Odds ratio, POR: Prevalence odds ratio, P: Prevalence, RR: Relative risk

\* 95% confidence intervals given within brackets



The outcomes of the published meta-analyses have to be interpreted with caution, as different assumptions were made about the prevalence of non-smokers in the different cohorts, which was caused by the lack of explicit data on former smokers and non-smokers. Consequently, subjects not identified as smoker were considered as non-smoker. If data on former smokers were available, they were grouped partially with current smokers (42) and partially with non-smokers (40, 43). The meta-analyses used also different indicators for the evaluation and interpretation of the studies. A common limitation to all presented meta-analyses is the fact that most of the data stem from retrospective case studies, which did not consider confounding variables. Simons et al. identified a number of issues, which could introduce bias respectively complicate at least the interpretation of the observational studies (44). The selection of the subjects included in the published studies occurred according to criteria such as hospitalisation, development of severe pneumonia, or other endpoints. Additionally, the double accounting of patient data in different studies cannot be excluded, e.g. the two publications of Guan et al. comprise likely overlapping study cohorts (13, 14). The same is expected for data published by the CDC, and by Goyal et al., which concern geographically overlapping areas (30, 37).

The characteristics of the analysed cohorts as well as the reported smoking status is summarized in Table 2. All cohorts had lower numbers of smokers in comparison to the number of smokers in the related population. The calculated prevalence ratios (PR) were with two exceptions significantly below unity. This data is irritating, as it is reasonable to expect that outcomes from COVID-19 infection are worse for smokers, as is the case in other acute respiratory infections.

Patients in most of the studied cohorts were of high average age, triggering the question whether smoking prevalence data of the general population forms a valid basis for making comparisons. Although none of the studies explicitly claimed that the investigated cohorts are representative for the general population. Providing further evidence that the studied cohorts reflect health related conditions of the general population could be useful for substantiating the potential effect of nicotine uptake on the progression of COVID-19 in hospitalised patients.

This question was approached by investigating whether data on comorbidities reported in the cohort studies correlate with the related data of the underlying populations. Data on the non-communicable diseases hypertension, diabetes mellitus, and chronic obstructive pulmonary disease (COPD) were extracted from the cohort studies and combined with published prevalence data for these illnesses. This allowed estimating the theoretical number of comorbidity cases in the studied cohorts if prevalence rates of the general population were assumed. The investigation was centred on 25 studies forming the basis for early meta-analyses, which partially identified a potentially beneficial effect of smoking/nicotine intake.

Table 2: Observed and expected smoker, prevalence ratio (PR), and probability that observed population is representative for general population

Author	Country	Obs.	Male	Female	Smoker obs.	Smoker ratio obs.	95% CI, LL	95% CI, UL	Smoker exp.	Smoker ratio exp.	PR	P-Value
		#			#				#			
Zhang et al. (16)	CN	133	0.507	0.493	2	0.015	0.002	0.053	37	0.278	0.05	0.000
Huang et al. (18)	CN	41	0.732	0.268	3	0.073	0.015	0.199	16	0.390	0.19	0.000
Guan, Ni et al. (14)	CN	1099	0.582	0.418	137	0.125	0.106	0.146	346	0.315	0.40	0.000
Yang et al. (15)	CN	52	0.673	0.327	2	0.038	0.005	0.131	19	0.365	0.11	0.000
Guan, Liang et al (13)	CN	1590	0.569	0.424	111	0.070	0.058	0.084	489	0.308	0.23	0.000
Chen et al. (19)	CN	274	0.624	0.376	7	0.026	0.011	0.053	92	0.336	0.08	0.000
Liu et al. (17)	CN	78	0.500	0.500	5	0.064	0.021	0.143	21	0.269	0.24	0.000
Zhou et al. (20)	CN	191	0.623	0.377	11	0.058	0.029	0.101	64	0.335	0.17	0.000
Zhang, Cai et al. (23)	CN	645	0.509	0.491	41	0.064	0.046	0.086	179	0.278	0.23	0.000
Wang et al. (27)	CN	125	0.568	0.432	16	0.128	0.075	0.200	38	0.304	0.42	0.000
Wan et al. (22)	CN	135	0.533	0.467	9	0.067	0.031	0.123	39	0.289	0.23	0.000
Shi et al. (24)	CN	474	0.532	0.468	40	0.084	0.061	0.113	141	0.297	0.28	0.000
Feng et al. (28)	CN	454	0.569	0.431	44	0.097	0.071	0.128	147	0.324	0.30	0.000
Ji et al. (29)	CN	208	0.563	0.438	19	0.091	0.056	0.139	63	0.303	0.30	0.000
Li et al. (26)	CN	544	0.509	0.491	41	0.075	0.054	0.100	153	0.281	0.27	0.000
Mo et al. (21)	CN	155	0.555	0.445	6	0.039	0.015	0.083	47	0.303	0.13	0.000
Kim et al. (25)	KR	28	0.536	0.464	5	0.179	0.061	0.369	6	0.214	0.83	0.855
Goyal et al. (30)	US	393	0.606	0.394	20	0.051	0.031	0.078	83	0.211	0.24	0.000
CDC (37)	US	7162	-	-	96	0.013	0.011	0.016	1411	0.197	0.07	0.000
Gold et al. (36)	US	305	0.495	0.505	16	0.052	0.030	0.083	61	0.200	0.26	0.000
Miyara et al. (1)*	FR	341	0.601	0.399	21	0.062	0.039	0.093	89	0.259	0.24	0.000
Miyara et al. (1)**	FR	132	0.460	0.547	13	0.098	0.054	0.160	35	0.252	0.39	0.000
Miyara et al. (1)***	FR	473	0.560	0.442	34	0.072	0.050	0.099	125	0.259	0.28	0.000
Han et al. (31)	CN	17	0.353	0.647	3	0.176	0.038	0.434	3	0.176	1.00	1.000
Jin et al. (32)	CN	651	0.492	0.508	41	0.063	0.046	0.084	176	0.270	0.23	0.000

<b>Lian et al. (33).</b>	CN	788	0.516	0.484	54	0.069	0.052	0.089	222	0.282	0.24	0.000
<b>Yao et al. (34)</b>	CN	108	0.398	0.602	4	0.037	0.010	0.092	24	0.222	0.17	0.000
<b>Zhang, Ouyang et al. (35)</b>	CN	120	0.358	0.642	6	0.050	0.019	0.106	24	0.200	0.25	0.000

<sup>1</sup> hospitalized patients; <sup>2</sup> non-hospitalized patients; <sup>3</sup> all patients;

PR: prevalence ratio; obs.: observed; exp.: expected; 95% CI: 95 % confidence interval; LL: lower limit; UL: upper limit

## Exploratory data analysis

Information on the smoking status and comorbidities of the investigated cohorts were compiled from the respective publications. Prevalence ratios for smoking were calculated for the studied cohorts taking into account the actual number of subjects for which information on smoking status was specified. The expected prevalence ratios for active smokers were determined for the given cohort sizes respecting gender and country dependent differences. Actual data on the smoking status and prevalence of hypertension, diabetes mellitus and COPD in the respective countries was retrieved from public sources (Table 3). Hypertension rates for Chinese cohorts were adjusted for gender and geographical region applying rates specified in the electronic supplement of Wang et al. (45). The expected hypertension prevalence of subjects from 30 respectively 31 provinces were estimated with hypertension rates for the general Chinese population, whereas averages of province dependent rates were used in case data comprised subjects from more than one province (45). Country-specific diabetes prevalence data were retrieved for China, France and Korea from the International Diabetes Federation (IDF), which however did not allow discriminating according to gender, and from Virani et al. for the USA (46, 47). Chronic obstructive pulmonary disease (COPD) occurs mainly at elderly people. For this reason prevalence data are often provided only for certain age groups, such as Chinese and Korean adults above 40 years of age (48, 49). Applying them to the general population will likely overestimate the prevalence of COPD in that country. Additionally, available prevalence data are associated with significant uncertainties and might be subject to geographical variations (50). It should also be noted that some COPD prevalence data is already more than a decade old and might not anymore reflect the current situation (51). Acknowledging these limitations, they might nonetheless be applicable to the studied cohorts as the average age of the cohorts was mostly high as well. Most recent US countrywide prevalence data was preferred to older federal state specific prevalence data (50, 52).

Table 3: Smoking prevalence and prevalence of comorbidities in the countries of the studied cohorts

	<b>Smoking</b>		<b>Hypertension</b>		<b>Diabetes mellitus</b>		<b>COPD</b>	
<b>Data sources</b>	(53-56)		(45, 47, 57, 58)		(46, 47)		(48-51)	
<b>Gender</b>	M	F	M	F	M	F	M	F
<b>Country/Region</b>	%	%	%	%	%	%	%	%
FR	28.2	22.9	36.5	25.2	7.6		7.5	
KR	35.8	6.5	35.0	22.9	9.2		21.6	5.8
US	25.8	14.1	49.0	42.8	10.9	8.9	6.4	
CN	52.1	2.7			10.9		19	8.1
CN- Hubei			19.7	16.5				
CN- Chongqing			20.4	20.7				
CN- Zhejiang			25.4	21.0				
CN- Anhui, Hubei, Shanghai			23.8	21.3				
CN- 30/31 provinces			24.5	21.9				

M: male; F: female

FR: France; KR: South Korea; US: United States of America; CN: People's Republic of China

Expected occurrence figures and occurrence rates were calculated for the studied cohorts taking into account the respective cohort size and prevalence data given in Table 3. Occurrence figures were rounded to the next integer. Occurrence rates calculated for the studied cohorts were complemented by their 95% confidence intervals. Statgraphics Centurion 18 (Statgraphics Technologies Inc) was applied for that purpose, as well as for deriving respective probability values.

## Findings

Exploratory data analysis confirmed the mismatch of the observed number of smokers with the number of smokers expected for the cohort size in the general population. Prevalence ratios for smoking were with the exception of two studies significantly below one and p-values usually close to zero. These observations formed the basis for the hypothesis that nicotine uptake might have a protective effect against symptomatic COVID-19. However, the figures demonstrate only a difference between the number of observed smokers and the number of smokers expected for the particular cohort. Nonetheless, the plausibility of the hypothesis of a protective effect of nicotine against symptomatic COVID-19 would be supported if it could be demonstrated that prevalence in the general population of other medical conditions is reflected in the published cohort data.

The investigation of hypertension, diabetes, and COPD revealed for many cohorts a statistically significant discrepancy between the observed prevalence and the prevalence in the general population. As for smoking, the observed prevalence was frequently lower than the one expected in the general population. A compilation of prevalence ratios is provided in Table 4. Figures in red indicate at the 95 % confidence level a significantly lower prevalence observed in the studied cohorts compared to the prevalence expected in the general population of the respective country, figures in green indicate the opposite, and figures in black were not statistically significant (95% confidence level) different from the general population.

The power of the applied binomial test is strongly influenced by the size of the cohort. The smaller it is the lower is the power of the test, which explains the lack of statistical significance of some prevalence ratios largely different from one in either direction (Table 4). The situation changes with large cohort sizes, for which reason it is even more astonishing that the patients in the largest cohorts did not match the prevalence for any of the four features in the general population. This, however, must be interpreted with caution, as some cohort data might not be independent from each other, e.g. papers published by Lian et al., Jin et al., and Zangh, Cai et al. comprise patient data from the same hospital in Hangzhou (province Zhejiang, China) (23, 32, 33); this is also likely the case for papers published by Guan, Ni et al. and Guan, Liang et al. (13, 14). Even if the potential repetition of patient data is taken into account, the health status of these cohorts appear to be considerably better than in the underlying population, despite suffering from symptomatic COVID-19. The same is observed for patients from the United States, for which information on two comorbidities was not specific enough to be included in this evaluation. As mentioned by the authors, the quality of data might be compromised by the rapid evolution of the pandemic, urgency of medical interventions, and lack of resources, which might explain the lack of complete data on underlying health conditions in more than 94 % of the more than 122000 studied case reports. Therefore, representativeness of the data reported in the different studies for the general population cannot be presumed and caution has to be exercised in the interpretation of the outcomes of some meta-analyses due to this limitation and the mentioned potentially double accounting of patient data.

The limited agreement of the reported cohort data with the general population in terms of prevalence of underlying health conditions other than smoking demonstrates indirectly that these patients most likely do not reflect the situation of the general population. In the absence of specifically designed studies, any hypothesis on the effect of nicotine on symptomatic COVID-19 remains speculative. The number of potentially confounding variables would require a multivariate statistical approach and large cohort sizes for providing clarity on the significance of potential effects. However, the structure of the published aggregated data permits only univariate approaches. As such, the hypothesis of a potentially protective effect of nicotine on symptomatic COVID-19 cannot be verified. Consequently, specially designed studies are warranted for elucidating the effect of smoking/nicotine uptake on the development of symptomatic COVID-19.

Table 4: Compilation of prevalence ratios (PR) of the observed prevalence with the prevalence in the respective general population

Author	Country	Obs. #	Age* y	PR			
				Smoking	HT	Diabetes	COPD
Zhang et al. (16)	CN	133	57	0.05	1.66	1.11	0.11
Huang et al. (18)	CN	41	49	0.19	0.78	1.79	0.15
Guan, Ni et al. (14)	CN	1099	47	0.40	0.64	0.68	0.08
Yang et al. (15)	CN	52	59.7	0.11		1.59	0.50
Guan, Liang et al (13)	CN	1590	48.9	0.23	0.73	0.75	0.11
Chen et al. (19)	CN	274	62	0.08	1.83	1.57	
Liu et al. (17)	CN	78	38	0.24	0.57	0.59	0.19
Zhou et al. (20)	CN	191	56	0.17	1.64	1.73	0.21
Zhang, Cai et al. (23)	CN	645	45.2	0.23	0.67	0.68	0.01
Wang et al. (27)	CN	125	38.8	0.42			
Wan et al. (22)	CN	135	47	0.23	0.47	0.82	0.21
Shi et al. (24)	CN	474	46	0.28	0.87	0.55	
Feng et al. (28)	CN	454	53	0.30	1.04	0.94	
Ji et al. (29)	CN	208	44	0.30			
Li et al. (26)	CN	544	60	0.27	1.67	1.39	0.23
Mo et al. (21)	CN	155	54	0.13	1.31	0.89	0.23
Kim et al. (25)	KR	28	42.6	0.83	0.00	0.78	0.00
Goyal et al. (30)	US	393	62.2	0.24	1.08	2.49	0.80
CDC	US	7162		0.07	0.03		
Gold et al. (36)	US	305	60	0.26	1.47	4.01	0.82
Miyara et al. (1) <sup>1</sup>	FR	341		0.24	1.29	3.64	1.05
Miyara et al. (1) <sup>2</sup>	FR	132		0.39	0.37	0.66	0.19
Miyara et al. (1) <sup>3</sup>	FR	473		0.28	1.04	2.78	0.80
Han et al. (31)	CN	17	40	1.00	0.33	1.08	0.49
Jin et al. (32)	CN	651	~45	0.23	0.66	0.68	0.01
Lian et al. (33).	CN	788		0.24	0.69	0.66	0.03
Yao et al. (34)	CN	108	52	0.17	0.83	0.43	0.45**
Zhang, Ouyang et al. (35)	CN	120	45.4	0.25	0.90	0.54	0.28

\*Mean or median;

\*\* comprises bronchiectasis, COPD, and asthma

<sup>1</sup> hospitalized patients; <sup>2</sup> non-hospitalized patients; <sup>3</sup> all patients;

PR: prevalence ratio; obs.: observed; y: years; HT: hypertension

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